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Intrauterine environment and breast cancer risk in a population-based case-control study in Poland

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High estrogen exposure *in utero* may increase breast cancer risk later in life. However, studies of the associations between perinatal factors presumed to affect the fetal hormonal environment and breast cancer risk are inconsistent. We used data from a population-based case-control study of 2,386 incident breast cancers and 2,502 controls in Poland to evaluate risks associated with various perinatal characteristics. After adjusting for confounders, we found a significant trend ($p = 0.01$) of breast cancer risk with birth weight (OR = 1.54, 95% CI 1.08–2.19 for birth weights >4,000 g *vs.* <2,500 g). Subjects with a high birth order (≥6) were at reduced risk (OR = 0.81, 0.61–1.06) when compared with first born subjects. Birth weight was somewhat a stronger risk predictor among subjects whose cancers were diagnosed at 50 years of age or older (OR = 1.84, 1.19–2.85) than among those with cancers diagnosed at younger ages (OR = 1.14, 0.61–2.12). Subjects whose mothers smoked during their pregnancies were at slightly higher risk than those who never smoked (OR = 1.21, 0.99–1.47), but the risk was similar to mothers who only smoked at other times (OR = 1.22, 0.81–1.84). Breast cancer risk was not related to paternal smoking, maternal age, gestational age or twin status. Our results add support to the growing evidence that some perinatal exposures may relate to breast cancer risk. Additional studies are needed to confirm associations and clarify the biologic mechanisms underlying these associations.
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Key words: breast cancer; perinatal factors; hormones; *in utero* exposures

Increased exposure *in utero* to maternal estrogen may affect fetal mammary development, which in turn may increase breast cancer risk in adulthood.[1] Studies reported to date have yielded conflicting results with respect to whether birth weight, gestational age, maternal age, twinship, and other factors are associated with hormone levels *in utero* and breast cancer risk.[2] Defining the associations between these factors and breast cancer is important for understanding the etiology of this tumor and could have implications for assessing the disease burden in populations. Notably, in developed nations, maternal age has increased and twinning has become common among women receiving certain fertility treatments, whereas the percentage of children born at low birth weight has risen.[3,4]

To clarify the relationship of perinatal factors and the subsequent risk for breast cancer, we analyzed self-reported data from a large population-based case-control study recently conducted in Poland.

Material and methods

Study subjects and data collection

The U.S. National Cancer Institute in collaboration with the M. Sklodowska-Curie Institute of Oncology and Cancer Center in Warsaw and the Institute of Occupational Medicine in Lodz conducted a population-based breast cancer case-control study in Warsaw and Lodz in Poland. Eligible cases ($n = 3,037$) consisted of all women 20–74 years of age who were newly diagnosed with either histologically or cytologically confirmed incident *in situ* or invasive breast cancer. Subjects were recruited through rapid case ascertainment systems organized at 5 participating hospitals in the 2 cities for the period 2000–2003. Participating hospitals covered ~90% of eligible cases in these cities. Periodic reviews of information from the Cancer Registry in Warsaw were used to identify cases that were missed by the Rapid Identification System, with 288 cases (12.1%) identified through this system. Potential controls were identified through the Polish Electronic System of Population Evidence, a complete enumeration system of residents of the 2 cities. Eligible controls included 3,639 women who did not have a history of breast cancer, frequency matched to the anticipated distribution of the cases by 5-year age group and city of residence. This study was approved by appropriate review boards at the National Cancer Institute, Bethesda, MD, and participating institutions and all participating subjects provided informed consent.

Eligible study subjects were approached for personal interviews by trained interviewers, with 2,386 cases (78.6%) and 2,502 controls (68.8%) agreeing to participate. The reasons for nonparticipation were refusal (17.6% of cases, 24.1% of controls), inability to locate (2.1% cases, 6.5% controls) and other causes, including subjects' death (1.7% cases, 0.6% controls). Interviews covered all commonly accepted and a variety of postulated risk factors. Medical records of cases were abstracted to obtain information on disease characteristics, including stage at diagnosis, histology and hormone receptor status.

Information collected on perinatal characteristics included gestational age of the subject at time of birth (<37 weeks, ≥37 weeks or missing), biological mother's age at subject's birth, birth order and birth weight (number of grams if known or defined categorically as <2,500 g, 2,500–4,000 g, >4,000 g or missing). Subjects were also asked about membership in a twin pair and those who responded affirmatively were further questioned about zygosity and sibling gender. We also obtained information on the smoking patterns of any regular smokers who had lived with the study subjects. This information was used to determine whether the mother or father had likely been smoking during the time that the study subject was *in utero*.

Statistical analysis

Multiple logistic regression analysis was used to derive crude and adjusted estimates of odds ratios (OR) and associated 95% confidence intervals (CI). Education (<high school, high school graduate or beyond, missing), age at menarche (<13, 13, 14, 15, ≥16 years, missing), age at menopause (premenopausal, <45, 45–

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TABLE I – DEMOGRAPHIC AND REPRODUCTIVE CHARACTERISTICS OF SUBJECTS IN THE POLISH BREAST CANCER CASE-CONTROL STUDY

		Cases (n = 2,386)	Controls (n = 2,502)	p-value
Age	Mean (SD)	55.8 (10.0)	55.9 (10.1)	0.93
Age at menarche	Mean (SD)	13.5 (1.7)	13.7 (1.7)	<0.01
Age at menopause	Mean (SD)	49.6 (4.6)	49.2 (5.0)	<0.01
Age at first full-term pregnancy among parous women	Mean (SD)	24.4 (5.6)	23.6 (4.2)	<0.01
Number of full-term pregnancies among parous women	Mean (SD)	1.6 (0.9)	1.8 (0.9)	<0.01
Education	≥College, *N* (%)	818 (34.6)	586 (23.6)	<0.01
Marriage	Not married, *N* (%)	141 (6.0)	130 (5.2)	0.27
Site of recruitment (Lodz *vs*. Warsaw)	Lodz, *N* (%)	838 (35.1)	914 (36.5)	0.30
Menopausal status	Postmenopausal women, *N* (%)	1,764 (74.1)	1,720 (68.8)	<0.01
Ever a full-term pregnancy	Nulliparous women, *N* (%)	216 (9.1)	204 (8.2)	0.26
Current body mass index	>30kg/m^2, *N* (%)	644 (27.1)	776 (31.1)	<0.01
Family history of breast cancer among first degree relatives	Yes, *N* (%)	248 (10.4)	146 (5.8)	<0.01
Prior screening mammogram	Yes, *N* (%)	1,462 (62.3)	1,347 (54.3)	<0.01

Numbers of participants with missing data are as follows: 0 for age, 35 for education, 41 for marriage, 0 for site of recruitment, 52 for age at menarche, 7 for menopausal status, 145 for age at menopause, 0 for ever a full-term pregnancy, 207 for age at first full-term pregnancy, 0 for number of full-term pregnancies, 14 for current body mass index, 1 for family history of breast cancer and 60 for prior screening mammogram.

49, 50–54, ≥55 years, missing), family history of breast cancer among first degree relatives (no, yes, missing), age at first full-term pregnancy (none, <20, 20–24, 25–29, ≥30 years, missing), number of full-term pregnancies (0, 1, 2, ≥3), prior screening mammogram (no, yes, missing) and body mass index at time of diagnosis (BMI, weight in kg/height in m^2) (< 25, 25–30, >30, missing) were considered as potential confounders of the perinatal risk factors of interest. The effects of various modifying factors, including age at diagnosis, were also considered. Missing values for all perinatal factors and covariates were included in the analyses to avoid losing subjects due to nonresponse.

Results

Characteristics of the 2,386 breast cancer cases and 2,502 controls are shown in Table I. The mean age of the subjects was similar between the cases (55.8 years) and controls (55.9 years). Cases were significantly better educated than controls. Cases were also more likely than controls to be postmenopausal and to have somewhat later average ages at menopause. Cases also had significantly earlier ages at menarche, later ages at first birth and fewer full-term pregnancies than controls. Controls had significantly higher current BMI than cases. Significantly greater proportions of cases than controls reported a prior screening mammogram, as well as a family history of breast cancer.

Table II presents ORs and 95% CI for the associations between perinatal risk factors and breast cancer risk. A significant positive trend between heavier birth weight and breast cancer risk was found (p for trend = 0.01). Birth weights over 4,000 g were associated with a significantly increased risk compared to weights less than 2,500 g (OR = 1.54, 95% CI 1.08–2.19). There was no trend in risk with the birth order of the study subject, although those with a birth order of 6 or more were at a somewhat reduced risk (OR = 0.81, 95% CI 0.61–1.06). No trend in risk was observed with either maternal age or gestational age. Twinship (all or stratified by zygosity or twin gender) was related to modest decreases in breast cancer risk, although based on relatively small numbers of twins. Although the risks for daughters were somewhat elevated if their mothers had ever smoked, there was no variation according to whether the subject had been exposed to cigarette smoke *in utero* (respective ORs of 1.21 (0.99–1.47) *vs*. 1.22 (0.81–1.84)). Paternal smoking during the time the subject was *in utero* was unrelated to risk.

Given that there may be complex interrelationships according to perinatal factors, we examined various relationships according to birth order (first born *vs*. later born child) (Table III). Although the relationship with birth weight showed a slightly stronger trend among first born subjects, the p for interaction was not statistically significant. No differences in the associations between the 2 groups were observed for maternal age or for gestational age or twin status (data not shown).

Table IV shows the relationship of perinatal risk factors according to whether breast cancer was diagnosed before or after 50 years of age. The association with birth weight was more pronounced among women diagnosed at 50 years of age or later than among women diagnosed at earlier ages (respective ORs and 95% CIs for >4,000 g *vs*. <2,500 g were 1.84, 1.19–2.85 *vs*. 1.14, 0.61–2.12), although the difference in ORs was not statistically significant. Birth order and maternal age relationships were similar for the younger and older subjects. In contrast to the results for the total series, twin membership was associated with an increased risk for early onset breast cancers (OR=1.99, 95% CI 0.84–4.68, based on 17 exposed cases and 9 exposed controls), and a significantly reduced risk for the later onset breast cancers (OR=0.50, 95% CI 0.29–0.86). This difference was statistically significant (p-interaction = 0.006). Relationships with gestational age also showed some incongruity between the younger and older subjects, but the difference was not significant. Breast cancer risk was not related to maternal or paternal smoking in either age group (data not shown).

Discussion

Our analysis of data from a large population-based case-control study provides additional evidence that perinatal factors may affect breast cancer risk decades later. Although the risk associations that we identified were relatively modest, they provide impetus for further research to define the relationships between maternal factors, hormones, fetal development and cancer risk.

Our study supported an association between heavier birth weight and breast cancer risk. A positive association with birth weight has been found in case-control, cohort, record linkage and twin studies,[5–15] although a number of studies have failed to note a relationship.[16–25] Of the previous investigations that reported significant dose-response relationships, 3 noted stronger effects for early onset breast cancer,[5,7,13] whereas we observed the most pronounced effect for late onset cancers. Some authors have noted a J-shaped risk relation between a woman's birth weight and adult breast cancer risk,[5,6,8,14] especially for earlier-onset breast cancers[5]; although in only 1 of these studies was the relationship statistically significant.[14] The majority of these investigations, however, analyzed their data according to 5 birth weight categories, with 2,500–2,599,[5,6] 3,000–3,499[14] or 2,500–3,499[8] g as the referent categories. Because of the large proportion of women in our study

TABLE II – ASSOCIATIONS OF PERINATAL CHARACTERISTICS WITH BREAST CANCER RISK

	Number of cases	Number of controls	OR (95% CI)[1]
Birth weight			
< 2500 g	100	121	1.00 (reference)
2500–4000 g	1,510	1,559	1.22 (0.92–1.62)
> 4000 g	181	145	1.54 (1.08–2.19)
Missing	595	677	
Test for trend			$p = 0.01$
Birth order of subject			
1	762	770	1.00 (reference)
2	651	638	1.07 (0.91–1.24)
3–5	665	741	0.99 (0.85–1.15)
≥6	108	159	0.81 (0.61–1.06)
Missing	200	194	
Test for trend			$p = 0.31$
Maternal age			
< 20 years	88	101	1.00 (reference)
20–24 years	690	758	1.02 (0.75–1.39)
25–29 years	737	751	1.07 (0.79-1.46)
30–34 years	466	430	1.16 (0.84-1.60)
≥ 35 years	330	397	0.91 (0.66-1.27)
Missing	75	65	
Test for trend			$p = 0.76$
Gestational age			
≥37 weeks	1,853	1,927	1.00 (reference)
<37 weeks	103	102	1.01 (0.75–1.34)
Missing	430	473	
Multiple birth			
Singleton	2,300	2,423	1.00 (reference)
Twin	38	53	0.76 (0.49–1.16)
Missing	48	26	
Multiple birth by zygosity			
Singleton	2,300	2,423	1.00 (reference)
Monozygotic twin	27	32	0.90 (0.53–1.52)
Dizygotic twin	7	13	0.58 (0.23–1.47)
Missing information on zygosity	4	8	
Missing information on twinning	48	26	
Multiple birth by sex of twin			
Singleton	2,300	2,423	1.00 (reference)
Twin with sister	23	31	0.79 (0.46–1.38)
Twin with brother	13	22	0.60 (0.30–1.22)
Missing sex information	2	0	
Missing twin information	48	26	
Maternal smoking while subject *in utero*			
Never smoked	2,061	2,233	1.00 (reference)
Nonsmoking during pregnancy	56	43	1.22 (0.81–1.84)
Smoking during pregnancy	263	221	1.21 (0.99–1.47)
Missing	6	5	
Likelihood ratio test for trend			$p = 0.05$
Paternal smoking while subject *in utero*			
Never smoked	1,435	1,517	1.00 (reference)
Nonsmoking during pregnancy	74	61	1.13 (0.79–1.61)
Smoking during pregnancy	852	916	0.96 (0.85–1.09)
Missing	25	8	
Test for trend			$p = 0.53$

[1]The ORs and 95% CIs were adjusted for the following variables: age, education, age at menarche, menopausal status and age at menopause, age at first full-term pregnancy, number of full-term pregnancies, family history of breast cancer among first degree relatives, mammography screening and current body mass index.

who could not recall a precise birth weight, we had to rely on categorical responses, which were collected as only 3 categories (<2,500, 2,500–4,000, >4,000 g). This may have hindered our ability to detect a J-shaped relationship, had it existed.

Although it has been postulated that *in utero* exposure to higher maternal estrogen concentrations might explain the association with birth weight,[26,27] some studies have failed to identify a relationship between birth weight and fetal estrogen levels.[27] This has prompted suggestions that other biologic mechanisms, including nonestrogenic hormones and insulin-like growth factors,[28,29] might account for birth weight effects. In addition, 1 study found that associations with birth weight and breast cancer risk disappeared after adjustment for birth length and head circumference.[13]

Some, although not all, studies have shown that pregnancy estrogens are highest during first pregnancies,[30,31] prompting speculations of a birth order effect on breast cancer risk. In our study, we found no difference in risk for birth order 1–5, but did observe a nonsignificantly reduced risk of birth order 6 or higher. Birth order has been found to be inversely associated with breast cancer risk in some studies,[5,16,22,23,32,33] but other studies have found no associations[6,14,18] or positive associations.[8,34] It is unclear whether our finding regarding birth order is a spurious one, reflecting either chance or misclassification error. However, the reduced risk associated with high birth orders was consistently observed for both younger and older onset breast cancers.

Some studies have found that daughters of older mothers are at increased breast cancer risk,[8,14,16,18,22,23,32,35,36] whereas other studies have not identified this association.[5,6,20,33,34,37–40] A proposed mechanism for this association has been altered pregnancy estriol levels among older mothers,[26,27] although some studies have failed to observe positive correlations with maternal or fetal

TABLE III – ASSOCIATIONS OF PERINATAL CHARACTERISTICS WITH BREAST CANCER RISK ACCORDING TO BIRTH ORDER OF SUBJECT

Factors	First birth			Later birth order			$p_{interaction}$
	Number of cases	Number of controls	OR (95% CI)[1]	Number of cases	Number of controls	OR (95% CI)[1]	
Birth weight							
<2500 g	36	37	1.00 (reference)	60	76	1.00 (reference)	
2500–4000 g	529	557	0.96 (0.58–1.58)	911	926	1.33 (0.92–1.90)	0.50[2]
>4000 g	56	36	1.66 (0.87–3.17)	111	103	1.41 (0.91–2.20)	0.14[3]
Missing	141	140		342	433		
Likelihood ratio test for trend			$p = 0.09$			$p = 0.17$	
Maternal age							
<20 years	69	79	1.00 (reference)	11	18	1.00 (reference)	
20–24 years	367	411	0.97 (0.67–1.41)	273	302	1.40 (0.64–3.05)	0.50[2]
25–29 years	234	197	1.24 (0.84–1.83)	463	508	1.38 (0.64–2.99)	0.15[3]
30–34 years	66	51	1.17 (0.70–1.96)	374	344	1.60 (0.74–3.49)	0.07[4]
≥35 years	23	26	0.86 (0.44–1.67)	285	340	1.24 (0.57–2.71)	0.10[5]
Missing	3	6		18	26		
Likelihood ratio test for trend			$p = 0.36$			$p = 0.80$	

[1]The ORs and 95% CIs were adjusted for the following variables: age, education, age at menarche, menopausal status and age at menopause, age at first full-term pregnancy, number of full-term pregnancies, family history of breast cancer among first degree relatives, mammography screening and current body mass index.–[2]Interaction between [perinatal factor] with the first and the second category and [birth order].–[3]Interaction between [perinatal factor] with the first and the third category and [birth order].–[4]Interaction between [perinatal factor] with the first and the fourth category and [birth order].–[5]Interaction between [perinatal factor] with the first and the fifth category and [birth order].

TABLE IV – PERINATAL CHARACTERISTICS ACCORDING TO AGE AT DIAGNOSIS OF BREAST CANCER

Factors	Age < 50			Age ≥ 50			$p_{interaction}$
	Number of cases	Number of controls	OR (95% CI)[1]	Number of cases	Number of controls	OR (95% CI)[1]	
Birth weight							
< 2500 g	39	36	1.00 (reference)	61	85	1.00 (reference)	
2500–4000 g	518	536	0.90 (0.55–1.48)	992	1,023	1.40 (0.99–1.99)	0.10[2]
>4000 g	60	52	1.14 (0.61–2.12)	121	93	1.84 (1.19–2.85)	0.21[3]
Missing	81	101		514	576		
Likelihood ratio test for trend			$p = 0.54$			$p = 0.006$	
Birth order of subject							
1	235	238	1.00 (reference)	527	532	1.00 (reference)	
2	213	199	1.23 (0.94–1.61)	438	439	1.06 (0.88–1.27)	0.83[2]
3–5	186	214	1.00 (0.75–1.33)	479	527	1.01 (0.84–1.21)	0.76[3]
≥6	23	36	0.73 (0.40–1.33)	85	123	0.84 (0.61–1.14)	0.85[4]
Missing	41	38		159	156		
Likelihood ratio test for trend			$p = 0.24$			$p = 0.55$	
Maternal age							
<20 years	35	25	1.00 (reference)	53	76	1.00 (reference)	
20–24 years	228	262	0.69 (0.39–1.22)	462	496	1.29 (0.88–1.89)	0.06[2]
25–29 years	226	226	0.79 (0.45–1.42)	511	525	1.31 (0.89–1.92)	0.10[3]
30–34 years	129	110	0.91 (0.49–1.67)	337	320		0.15[4]
≥35 years	71	94	0.61 (0.32-1.15)	259	303	1.39 (0.94–2.06)	0.06[5]
Missing	9	8		66	57	1.19 (0.80–1.78)	
Likelihood ratio test for trend			$p = 0.90$			$p = 0.87$	
Gestational age							
≥37 weeks	576	597	1.00 (reference)	1,277	1,330	1.00 (reference)	0.11
<37 weeks	43	30	1.40 (0.84–2.33)	60	72	0.84 (0.59–1.21)	
Missing	79	98		351	375		
Multiple birth							
Singleton	674	713	1.00 (reference)	1,626	1,710	1.00 (reference)	0.006
Twin	17	9	1.99 (0.84–4.68)	21	44	0.50 (0.29–0.86)	
Missing	7	3		41	23		

[1]The ORs and 95% CIs were adjusted for the following variables: age, education, age at menarche, menopausal status and age at menopause, age at first full-term pregnancy, number of full-term pregnancies, family history of breast cancer among first degree relatives, mammography screening and current body mass index.–[2]Interaction between [perinatal factor] with the first and the second category and [age at diagnosis].–[3]Interaction between [perinatal factor] with the first and the third category and [age at diagnosis].–[4]Interaction between [perinatal factor] with the first and the fourth category and [age at diagnosis].–[5]Interaction between [perinatal factor] with the first and the fifth category and [age at diagnosis].

estrogen levels.[30,41] Our study provided little evidence of an effect on breast cancer risk of advancing maternal age.

Maternal age was also assessed, along with other perinatal factors, according to birth order (first born child *vs*. later birth), since at least 1 study has suggested that there may be complex interrelationships.[22] Our results, however, failed to show an effect of maternal age among either first or later born subjects. Similarly, birth order did not appear to significantly modify the observed relationships with birth weight.

No association with gestational age (<37 *vs*. ≥37 weeks) was seen with breast cancer risk in our study, consistent with several previous reports.[5,12,13,16,17,19,24] Other studies, with a definition of extreme prematurity (prior to 32 weeks) have reported both positive[18,42] and negative relationships,[8,9,15] although the biologic basis for these associations is obscure.

In a number of previous reports, an elevated risk of breast cancer has been seen for twins,[18,24,40,43–46] particularly for dizygotic twins or opposite sex twins.[18,40,43–45] However, the evidence has

been inconsistent, with some studies showing decreased risks,[5,47,48] or no association.[8,49] Some of these inconsistencies may be attributable to small numbers of twins in population-based studies. Our analysis of twins was limited by small numbers and yielded somewhat inconsistent results. Overall, twins were at non-significantly decreased risk irrespective of zygosity or sibling gender. However, further stratification by age showed increased risk for cancers diagnosed at younger ages and a reduced risk for cancers diagnosed at older ages (p-interaction = 0.006). It has been hypothesized that twins might be at higher risk of breast cancer because of higher estrogen and gonadotropin exposure *in utero*,[50,51] and that dizygotic twins might be exposed to even higher levels because of estrogen production by 2 placentas.[52] However, the difference in hormone levels between monozygotic and dizygotic pregnancies has not yet been established and the interactions between maternal, placental and fetal steroid production and exchange are not completely understood, especially since most studies have measured maternal rather than fetal hormones.[51] Thus, possible biologic mechanisms that might underlie any twinning associations remain uncertain.

Cigarette smoking during pregnancy has been hypothesized to reduce the risk of breast cancer in daughters, based on findings of low pregnancy estrogen levels among smokers.[53,54] Most studies, however, have failed to find any alterations in risk of daughters whose mothers[19,22,40,55,56] or fathers[22,55] smoked during pregnancy. Our results also provided little evidence for an effect of either maternal or paternal smoking, since the risks were not substantially different between those exposed *in utero* and those whose parents were non-smokers or who only smoked at other times.

Potential limitations in this study include sparse information on some perinatal characteristics and potential inaccuracy of self-reported factors. There was very little missing information with respect to maternal age, twin status or parental smoking, although there was considerable missing data on gestational age and birth weight. However, the amount of missing information in our study was similar to that found in other studies[57] and for most of our variables, there were no significant differences between cases and controls. The 2 exceptions were twinning and paternal smoking, but both of these variables involved small numbers of subjects with missing data.

A more major concern regarding our results was that perinatal characteristics were self-reported and might have been vulnerable to misclassification biases.[57,58] We were unable to check the validity of the reported perinatal factors, and it is possible that recall may have been differential between cases and controls. This could have led to under- or over-estimations of true associations, as has been shown previously for self-reported birth weight.[57] Misclassification is a particular concern for type of twinning. Although self-reports of zygosity would be accurate for opposite sex twins, zygosity may be unknown or incorrectly reported for a certain percentage of same-sex twins.[44] Although we would have no reason to expect recall of this variable to relate to breast cancer status, any misclassification, even if random, could have resulted in an attenuation of a real association.[44]

Our study did have several strengths, including its large size and population-based design. Many previous studies have been unable to adjust perinatal risk factors for other predictors of breast cancer risk, but we had extensive information on other established and speculative risk factors.

In summary, this case-control study showed that birth weight and possibly birth order may be associated with the risk of adult breast cancer, consistent with the hypothesis that the intrauterine environment influences subsequent breast cancer risk. These results support the hypothesis that pregnancy estrogens may play a role in adult breast cancer development. However, some perinatal factors believed to be associated with maternal estrogen levels, including maternal age, were not associated with risk. Of particular importance for future research will be studies that overcome the limitations of self-reported exposures, including those that rely on record linkage techniques with birth record datasets, and those that provide additional insights regarding possible biologic mechanisms.

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